USE OF MEDIUM CHAIN TRIGLYCERIDES FOR THE TREATMENT AND PREVENTION OF ALZHEIMER'S DISEASE AND OTHER DISEASES RESULTING FROM REDUCED NEURONAL METABOLISM

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to United States Provisional Application No. 60/200,980 filed May 1, 2000, entitled "Use of Medium Chain Triglycerides for the Treatment and Prevention of Alzheimer's Disease and Other Diseases Resulting from Reduced Neuronal Metabolism."

FIELD OF THE INVENTION

This invention relates to the field of therapeutic agents for the treatment of Alzheimer's Disease, and other diseases associated with reduced neuronal metabolism.

BACKGROUND OF THE INVENTION

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder, which primarily affects the elderly. There are two forms of AD, early-onset and late-onset. Early-onset AD is rare, strikes susceptible individuals as early as the third decade, and is frequently associated with mutations in a small set of genes. Late onset AD is common, strikes in the seventh or eighth decade, and is a mutifactorial disease with many genetic risk factors. Late-onset AD is the leading cause of dementia in persons over the age of 65. An estimated 7-10% of the American population over 65, and up to 40% of the American population greater than 80 years of age is afflicted with AD (McKhann et al., 1984; Evans et al. 1989). Early in the disease, patients experience loss of memory and orientation. As the disease progresses, additional cognitive functions become impaired, until the patient is completely incapacitated. Many theories have been proposed to describe the chain of events that give rise to AD, yet, at time of this application, the cause remains unknown. Currently, no effective prevention or treatment exists for AD. The only drugs to treat AD on the market today, Aricept® and Cognex®, are acetylcholinesterase inhibitors. These drugs do not address the underlying pathology of AD. They merely enhance the effectiveness of those nerve cells still able to function. Since the disease continues, the benefits of these treatments are slight.

Early-onset cases of AD are rare (~5%), occur before the age of 60 and are frequently associated with mutations in three genes, presenilin1 (PS1), presenilin2 (PS2) and amyloid precursor protein (APP) (for review see Selkoe, 1999). These early-onset AD cases exhibit cognitive decline and neuropathological lesions that are similar to those found in late-onset AD. AD is characterized by the accumulation of neurofibrillar tangles (NFT) and β–amyloid deposits in senile plaques (SP) and cerebral blood vessels. The main constituent of senile plaques is the β-amyloid peptide (Aß), which is derived from the APP protein by proteolytic processing. The presenilin proteins may facilitate the cleavage of APP. The Aß peptide is amyloidagenic and under certain conditions will form insoluble fibrils. However, the toxicity of Aß peptide and fibrils remains controversial. In some cases Aß has been shown to be neurotoxic, while others find it to be neurotrophic (for reviews see Selkoe, 1999). The cause of early-onset AD is hypothesized to be accumulation of aggregated proteins in susceptible neurons. Mutations in APP are hypothesized to lead to direct accumulation of fibrillar Aß, while mutations in PS1 or PS2 are proposed to lead to indirect accumulation of Aß. How a variety of mutations in PS1 and PS2 lead to increased Aß accumulation has not been resolved. Accumulation of aggregated proteins is common to many progressive neurodegenerative disorders, including Amyloid Lateral Sclerosis (ALS) and Huntington's disease (for review see Koo et al., 1999). Evidence suggests that accumulation of aggregated proteins inhibits cellular metabolism and ATP production. Consistent with this observation is the finding that buffering the energy capacity of neurons with creatine will delay the onset of ALS in transgenic mouse models (Klivenyi et al., 1999). Much of the prior art on AD has focused on inhibiting production of or aggregation of Aß peptides; such as U.S. Patent No. 5,817,626, U.S. Patent No. 5,854,204, and U.S. Patent No. 5,854,215. Other prior art to treat AD include, U.S. Patent No. 5,385,915 "Treatment of amyloidosis associated with Alzheimer disease using modulators of protein phosphorylation", patent U.S. Patent No. 5,538,983, "Method of treating amyloidosis by modulation of calcium." Attempts to increase neuronal survival by use of nerve growth factors have dealt with either whole cell, gene or protein delivery, such as described in U.S. Patent No. 5,650,148 "Method of grafting genetically modified cells to treat defects, disease or damage of the central nervous system", and U.S. Patent No. 5,936,078 "DNA and protein for the diagnosis and treatment of Alzheimer's disease."

The vast majority (~95%) of AD cases are late-onset, occurring in the seventh or eighth decade. Late-onset AD is not associated with mutations in APP, PS1 or PS2, yet exhibits neuropathological lesions and symptoms that are similar to those found in early-onset AD. Since late-onset AD is the most common form, it will be referred to herein as AD, while early-onset AD will be referred to as such. The similar neuropathology and outward symptoms of early-onset and late-onset AD have led to the "amyloid cascade hypothesis of AD" (Selkoe, 1994). This model holds that both early and late onset AD result from accumulation of toxic amyloid deposits. The model speculates that in early onset cases, amyloid accumulates rapidly, while in late onset, amyloid accumulates slowly. Much of the research on prevention and treatment of AD has focused on inhibition of amyloid accumulation. However, the amyloid cascade hypothesis remains controversial. Amyloid deposits may be a marker for the disease and not the cause. Translation of Dr. Alzheimer's original work on the neuropathology of AD, relates that he did not favor the view that senile plaques were causative. He states "These changes are found in the basal ganglia, the medulla, the cerebellum and the spinal cord, although there are no plaques at all in those sites or only isolated ones. So we have to conclude *that the plaques are not the cause of senile dementia but only an accompanying feature of senile involution of the central nervous system*." The italics are his own (Davis and Chisholm, 1999). Many years of research have not resolved this issue (for review of amyloid hypothesis see Selkoe, 1999, for counter argument see Neve et al., 1998). Since the present invention addresses the decreased neuronal metabolism associated with AD, it does not rely on the validity of the amyloid cascade hypothesis.

Several genetic risk factors have been proposed to contribute to the susceptibility to late-onset AD. However, only allelic variation in the lipid transport molecule apolipoprotein E (apoE) has been reproducibly defined as a genetic risk factor for late onset AD. ApoE functions as a ligand in the process of receptor mediated internalization of lipid-rich lipoproteins. These lipoprotein complexes contain phosopholipids, triglycerides, cholesterol and lipoproteins. Several well-characterized allelic variations exist at the apoE locus, and are referred to as apoE2, E3 and E4. ApoE4 is associated with an increased risk of AD, while apoE2 and E3 are not. Increasing the dosage of the E4 allele increases the risk of AD, and lowers the age of onset. However, apoE4 is not an invariant cause of AD. Some individuals,

who are homozygous for the E4 allele, do not show AD symptoms even into the ninth decade (Beffert et al., 1998).

A prediction of the observation that apoE4 is associated with AD is that populations with a high prevalence of the E4 allele would also have a high incidence of AD. Yet, the opposite appears to be true. Geographically distinct populations have differing frequencies of apoE alleles. For example, the E4 variant is much more common in Africa versus the UK. In a study of black South Africans and Caucasians from Cambridge England, the apoE4 allele was present in 48% of Black South Africans compared to 20.8% of Caucasians (Loktionov et al, 1999). In fact, the E4 allele is widespread throughout Africa (Zekraoui et al, 1997). Studies on AD are difficult to do in developing countries, but the studies that have been done show a very low incidence of AD in African communities, 1% versus 6% in US populations (Hall et al, 1998). Even more striking is that the normally robust association between AD and apoE4 is absent in African cases (Osuntokun et al, 1995). This suggests that something is different between native Africans, and US citizens, who are largely of European descent. Perhaps the African populations have some other genetic factor that protects them from AD. This is unlikely, since the incidence of AD in a population of African-Americans from Indianapolis, Indiana USA (6.24%) was found to be much higher than an ethnically similar population in Ibadan, Nigeria (1.4%) (Hall et al, 1998). This suggests that the link between apoE4 and AD has some strong environmental component.

ApoE4 is the ancestral allele, it is most similar to the apoE found in chimpanzees and other primates, while the E2 and E3 alleles arose exclusively in the human lineage, (Hanlon and Rubinsztein, 1995). The changes in apoE were probably brought about by a change in diet in ancestral humans. The E2 and E3 alleles may have arisen in populations as an adaptation to agriculture (Corbo and Scacchi, 1999).

The metabolism of apoE4 in human circulation is different from the non-AD associated apoE3 allele (Gregg et al., 1986). The E4 allele is associated with unusually high levels of circulating lipoproteins (Gregg et al., 1986). In particular, the E4 allele results in decreased rates of VLDL clearance, which leads to higher levels of VLDL and LDL particles in the blood (Knouff, et al. 1999). VLDL and LDL particles contain higher levels of triglycerides than HDL particles. The increased levels of circulating VLDL in individuals carrying apoE4 is due to decreased fatty

acid utilization caused by preferential binding of apoE4 to chylomicron and VLDL particles. Prior art has suggested that apoE4 contributes to AD due to inefficient delivery of phospholipids to neurons (for review see Beffert et al., 1998). Yet, apoE4 also contributes to decreased triglyceride usage.

In the central nervous system (CNS), apoE plays a central role in the transportation and redistribution of cholesterol and lipids. The importance of apoE in the brain is highlighted by the absence of other key plasma apolipoproteins such as apoA1 and apoB in the brain (Roheim et al., 1979). ApoE mRNA is found predominantly in astrocytes in the CNS. Astrocytes function as neuronal support cells and can efficiently utilize fatty acids for energy. Since the brain lacks other apolipoproteins, it is uniquely dependent on apoE for lipid transport, including triglycerides. While prior art on apoE's role in AD has focused on phospholipid transport, apoE also delivers free fatty acids in the form of triglycerides to astrocytes. Fatty acids delivered by lipoproteins can be converted to ketone bodies by astrocytes for use as an alternative energy source to glucose. An alternative to the neuronal remodeling hypothesis, is that the preferential binding of apoE4 to VLDL particles prevents efficient astrocyte access to triglycerides. Decreased access to triglycerides results in decreased availability of fatty acids and decreased production of ketone bodies, and hence a decreased alternative energy source for cerebral neurons. This reduction in energy supplies may become critical when glucose metabolism in compromised.

Metabolism and Alzheimer's Disease At the time of this application, the cause of AD remains unknown, yet a large body of evidence has made it clear that Alzheimer's Disease is associated with decreased neuronal metabolism. In 1984, Blass and Zemcov proposed that AD results from a decreased metabolic rate in sub-populations of cholinergic neurons. However, it has become clear that AD is not restricted to cholinergic systems, but involves many types of transmitter systems, and several discrete brain regions. Positron-emission tomography has revealed poor glucose utilization in the brains of AD patients, and this disturbed metabolism can be detected well before clinical signs of dementia occur (Reiman et al., 1996; Messier and Gagnon, 1996; Hoyer, 1998). Additionally, certain populations of cells, such as somatostatin cells of the cortex in AD brain are smaller, and have reduced Golgi apparatus; both indicating decreased metabolic activity (for review see Swaab et al.

1998). Measurements of the cerebral metabolic rates in healthy versus AD patients demonstrated a 20-40% reduction in glucose metabolism in AD patients (Hoyer, 1992). Reduced glucose metabolism results in critically low levels of ATP in AD patients. Also, the severity of decreased metabolism was found to correlate with senile plaque density (Meier-Ruge, et al. 1994).

Additionally, molecular components of insulin signaling and glucose utilization are impaired in AD patients. Glucose is transported across the blood brain barrier and is used as a major fuel source in the adult brain. Consistent with the high level of glucose utilization, the brains of mammals are well supplied with receptors for insulin and IGF, especially in the areas of the cortex and hippocampus, which are important for learning and memory (Frolich et al., 1998). In patients diagnosed with AD, increased densities of insulin receptor were observed in many brain regions, yet the level of tyrosine kinase activity that normally is associated with the insulin receptor was decreased, both relative to age-matched controls (Frolich et al., 1998). The increased density of receptors represents up-regulation of receptor levels to compensate for decreased receptor activity. Activation of the insulin receptor is known to stimulate phosphatidylinositol-3 kinase (PI3K). PI3K activity is reduced in AD patients (Jolles et al., 1992; Zubenko et al., 1999). Furthermore, the density of the major glucose transporters in the brain, GLUT1 and GLUT3 were found to be 50% of age matched controls (Simpson and Davies 1994). The disturbed glucose metabolism in AD has led to the suggestion that AD may be a form of insulin resistance in the brain, similar to type II diabetes (Hoyer, 1998). Inhibition of insulin receptor activity can be exogenously induced in the brains of rats by intracerebroventricular injection of streptozotocin, a known inhibitor of the insulin receptor. These animals develop progressive defects in learning and memory (Lannert and Hoyer, 1998). While glucose utilization is impaired in brains of AD patients, use of the ketone bodies, beta-hydroxybutyrate and acteoacetate is unaffected (Ogawa et al. 1996).

The cause of decreased neuronal metabolism in AD remains unknown. Yet, aging may exacerbate the decreased glucose metabolism in AD. Insulin stimulation of glucose uptake is impaired in the elderly, leading to decreased insulin action and increased insulin resistance (for review see Finch and Cohen, 1997). For example, after a glucose load, mean plasma glucose is 10-30% higher in those over 65 than in

younger subjects. Hence, genetic risk factors for AD may result in slightly compromised neuronal metabolism in the brain. These defects would only become apparent later in life when glucose metabolism becomes impaired, and thereby contribute to the development of AD. Since the defects in glucose utilization are limited to the brain in AD, the liver is "unaware" of the state of the brain and does not mobilize fatty acids (see Brain Metabolism section below). Without ketone bodies to use as an energy source, the neurons of the AD patient brain slowly and inexorably starve to death.

Attempts to compensate for reduced cerebral metabolic rates in AD patients has met with some success. Treatment of AD patients with high doses of glucose and insulin increases cognitive scores (Craft et al., 1996). However, since insulin is a polypeptide and must be transported across the blood brain barrier, delivery to the brain is complicated. Therefore, insulin is administered systemically. Large dose of insulin in the blood stream can lead to hyperinsulinemia, which will cause irregularities in other tissues. Both of these shortcomings make this type of therapy difficult and rife with complications. Accordingly, there remains a need for an agent that may increase the cerebral metabolic rate and subsequently the cognitive abilities of a patient suffering from Alzheimer's disease.

Brain Metabolism The brain has a very high metabolic rate. For example, it uses 20 percent of the total oxygen consumed in a resting state. Large amounts of ATP are required by neurons of the brain for general cellular functions, maintenance of an electric potential, synthesis of neurotransmitters and synaptic remodeling. Current models propose that under normal physiologic conditions, neurons of the adult human brain depend solely on glucose for energy. Since neurons lack glycogen stores, the brain depends on a continuous supply of glucose from the blood for proper function. Neurons are very specialized and can only efficiently metabolize a few substrates, such as glucose and ketone bodies. This limited metabolic ability makes brain neurons especially vulnerable to changes in energy substrates. Hence, sudden interruption of glucose delivery to the brain results in neuronal damage. Yet, if glucose levels drop gradually, such as during fasting, neurons will begin to metabolize ketone bodies instead of glucose and no neuronal damage will occur.

Neuronal support cells, glial cells, are much more metabolically diverse and can metabolize many substrates, in particular, glial cells are able to utilize fatty acids

for cellular respiration. Neurons of the brain cannot efficiently oxidize fatty acids and hence rely on other cells, such as liver cells and astrocytes to oxidize fatty acids and produce ketone bodies. Ketone bodies are produced from the incomplete oxidation of fatty acids and are used to distribute energy throughout the body when glucose levels are low. In a normal Western diet, rich in carbohydrates, insulin levels are high and fatty acids are not utilized for fuel, hence blood ketone body levels are very low, and fat is stored and not used. Such a scenario explains the prevalence of obesity.

Current models propose that only during special states, such as neonatal development and periods of starvation, will the brain utilize ketone bodies for fuel. The partial oxidation of fatty acids gives rise to D-beta-hydroxybutyrate (D-3-hydroxybutyrate) and acetoacetate, which together with acetone are collectively called ketone bodies. Neonatal mammals are dependent upon milk for development. The major carbon source in milk is fat (carbohydrates make up less then 12% of the caloric content of milk). The fatty acids in milk are oxidized to give rise to ketone bodies, which then diffuse into the blood to provide an energy source for development. Numerous studies have shown that the preferred substrates for respiration in the developing mammalian neonatal brain are ketone bodies. Consistent with this observation is the biochemical finding that astrocytes, oligodendrocytes and neurons all have capacity for efficient ketone body metabolism (for review see Edmond, 1992). Yet only astrocytes are capable of efficient oxidation of fatty acids.

The body normally produces small amounts of ketone bodies. However, because they are rapidly utilized, the concentration of ketone bodies in the blood is very low. Blood ketone body concentrations rise on a low carbohydrate diet, during periods of fasting, and in diabetics. In a low carbohydrate diet, blood glucose levels are low, and pancreatic insulin secretion is not stimulated. This triggers the oxidation of fatty acids for use as a fuel source when glucose is limiting. Similarly, during fasting or starvation, liver glycogen stores are quickly depleted, and fat is mobilized in the form of ketone bodies. Since both a low carbohydrate diet and fasting do not result in a rapid drop of blood glucose levels, the body has time to increase blood ketone levels. The rise in blood ketone bodies provides the brain with an alternative fuel source, and no cellular damage occurs. Since the brain has such high energy demands, the liver oxidizes large amounts of fatty acids until the body becomes literally saturated in ketone bodies. Therefore, when an insufficient source of ketone

bodies is coupled with poor glucose utilization severe damage to neurons results. Since glial cells are able to utilize a large variety of substrates they are less susceptible to defects in glucose metabolism than are neurons. This is consistent with the observation that glial cells do not degenerate and die in AD (Mattson, 1998).

As discussed in the Metabolism and Alzheimer's Disease section, in AD, neurons of the brain are unable to utilize glucose and begin to starve to death. Since the defects are limited to the brain and peripheral glucose metabolism is normal, the body does not increase production of ketone bodies, therefore neurons of the brain slowly starve to death. Accordingly, there remains a need for an energy source for brain cells that exhibit compromised glucose metabolism in AD patients. Compromised glucose metabolism is a hallmark of AD; hence administration of such an agent will prove beneficial to those suffering from AD.

Medium Chain Triglycerides (MCT) The metabolism of MCT differs from the more common long chain triglycerides (LCT) due to the physical properties of MCT and their corresponding medium chain fatty acids (MCFA). Due to the short chain length of MCFA, they have lower melting temperatures, for example the melting point of MCFA (C8:0) is 16.7 °C, compared with 61.1 °C for the LCFA (C16:0). Hence, MCT and MCFA are liquid at room temperature. MCT are highly ionized at physiological pH, thus they have much greater solubility in aqueous solutions than LCT. The enhanced solubility and small size of MCT also increases the rate at which fine emulsion particles are formed. These small emulsion particles create increased surface area for action by gastrointestinal lipases. Additionally, medium chain 2-monoglycerides isomerize more rapidly than those of long chain length, allowing for more rapid hydrolysis. Some lipases in the pre-duodenum preferentially hydrolyze MCT to MCFA, which are then partly absorbed directly by stomach mucosa (Hamosh, 1990). Those MCFA which are not absorbed in the stomach, are absorbed directly into the portal vein and not packaged into lipoproteins. LCFA are packaged in chylomicrons and transported via the lymph system, while MCFA are transported via the blood. Since blood transports much more rapidly than lymph, the liver is quickly perfused with MCFA.

In the liver the major metabolic fate of MCFA is oxidation. The fate of LCFA in the liver is dependent on the metabolic state of the organism. LCFA are transported into the mitochondria for oxidation using carnitine palmitoyltransferase I.

When conditions favor fat storage, malonyl-CoA is produced as an intermediate in lipogenesis. Malonyl-CoA allosterically inhibits carnitine palmitoyltransferase I, and thereby inhibits LCFA transport into the mitochondria. This feedback mechanism prevents futile cycles of lipolysis and lipogenesis. MCFA are, to large extent, immune to the regulations that control the oxidation of LCFA. MCFA enter the mitochondria largely without the use of carnitine palmitoyltransferase I, therefore MCFA by-pass this regulatory step and are oxidized regardless of the metabolic state of the organism. Importantly, since MCFA enter the liver rapidly and are quickly oxidized, large amounts of ketone bodies are readily produced from MCFA.

Numerous patents relate to use of MCT. None of these patents relate to the specific use of MCT for treatment and prevention of Alzheimer's Disease. Patents such as U.S. Patent No. 4,528,197 "Controlled triglyceride nutrition for hypercatabolic mammals" and U.S. Patent No. 4,847,296 "Triglyceride preparations for the prevention of catabolism" relate to the use of MCT to prevent body-wide catabolism that occurs in burns and other serious injuries. Each patent described herein is incorporated by reference herein in its entirety.

SUMMARY OF THE INVENTION

The present invention provides a method of treating or preventing dementia of Alzheimer's type, or other loss of cognitive function caused by reduced neuronal metabolism, comprising administering an effective amount of medium chain triglycerides to a patient in need thereof. Administration may be oral or intravenous. The medium chain triglycerides may be emulsified, and may be coadministered with L-carnitine or a derivative of L-carnitine.

The present invention also provides a method of treating or preventing dementia of Alzheimer's type, or other loss of cognitive function caused by reduced neuronal metabolism, comprising administering an effective amount of free fatty acids derived from medium chain triglycerides to a patient in need thereof.

The present invention also provides a method of treating or preventing dementia of Alzheimer's type, or other loss of cognitive function caused by reduced neuronal metabolism, comprising administering an effective amount of a medium chain triglyceride prodrug to a patient in need thereof.

The present invention also provides a method of treating or preventing dementia of Alzheimer's type, or other loss of cognitive function caused by reduced neuronal metabolism, comprising administering an effective amount of a therapeutic agent which induces utilization of fatty acids and development of ketosis to a patient in need thereof.

The present invention further provides therapeutic agents for the treatment or prevention of dementia of Alzheimer's type, or other loss of cognitive function caused by reduced neuronal metabolism.

DETAILED DESCRIPTION OF THE INVENTION

It is the novel insight of this invention that medium chain triglycerides (MCT) and their associated fatty acids are useful as a treatment and preventative measure for AD patients. MCT are composed of fatty acids with chain lengths of between 5-12 carbons. A diet rich in MCT results in high blood ketone levels. High blood ketone levels will provide an energy source for brain cells that have compromised glucose metabolism via the rapid oxidation of MCFA to ketone bodies.

The background of this invention supports the present invention in the following ways. (1) Neurons of the brain can use both glucose and ketone bodies for respiration. (2) The neurons of Alzheimer's Disease patients have well documented defects in glucose metabolism. (3) Known genetic risk factors for Alzheimer's Disease are associated with lipid and cholesterol transport, suggesting defects in triglyceride usage may underlie susceptibility to Alzheimer's Disease. (4) A diet rich in MCT will lead to increased levels of blood ketone bodies and thereby provide energy to starving brain neurons. Hence, supplementation of Alzheimer's Disease patients with MCT will restore neuronal metabolism.

The present invention provides a method of treating or preventing dementia of Alzheimer's type, or other loss of cognitive function caused by reduced neuronal metabolism, comprising administering an effective amount of medium chain triglycerides to a patient in need thereof. Generally, an effective amount is an amount effective to either (1) reduce the symptoms of the disease sought to be treated or (2) induce a pharmacological change relevant to treating the disease sought to be treated. For Alzheimer's Disease, an effective amount includes an amount effective to: increase cognitive scores; slow the progression of dementia; or increase the life

expectancy of the affected patient. As used herein, medium chain triglycerides of this invention are represented by the following formula:

$$\begin{array}{c} H_2C\text{-}R1 \\ | \\ H_2C\text{-}R2 \\ | \\ H_2C\text{-}R3 \end{array}$$

wherein R1, R2 and R3 are fatty acids having 5-12 carbons in the carbon backbone. The structured lipids of this invention may be prepared by any process known in the art, such as direct esterification, rearrangement, fractionation, transesterification, or the like. For example the lipids may be prepared by the rearrangement of a vegetable oil such as coconut oil.

In a preferred embodiment, the method comprises the use of MCTs wherein R1, R2, and R3 are fatty acids containing a six-carbon backbone (tri-C6:0). Tri-C6:0 MCT are absorbed very rapidly by the gastrointestinal track in a number of model systems (Odle 1997). The high rate of absorption results in rapid perfusion of the liver, and a potent ketogenic response. Additionally, utilization of tri-C6:0 MCT can be increased by emulsification. Emulsification of lipids increases the surface area for action by lipases, resulting in more rapid hydrolysis. Methods for emulsification of these triglycerides are well known to those skilled in the art.

In another preferred embodiment, the invention provides a method of treating or preventing dementia of Alzheimer's type, or other loss of cognitive function caused by reduced neuronal metabolism, comprising administering an effective amount of free fatty acids, which may be derived from medium chain triglycerides, to a patient in need thereof. Such fatty acids are referred to herein as free medium chain fatty acids, or free fatty acids. Because MCT are metabolized to produce medium chain fatty acids, which are oxidized, the administration of free fatty acids and/or ketone bodies have the same effect as the administration of MCT themselves.

In another preferred embodiment, the invention comprises the coadministration of emulsified tri-C6:0 MCT and L-carnitine or a derivative of L-carnitine. Slight increases in MCFA oxidation have been noted when MCT are combined with L-carnitine (Odle, 1997). Thus in the present invention emulsified tri-C6:0 MCT are combined with L-carnitine at doses required to increase the utilization of said MCT. The dosage of L-carnitine and MCT will vary according to the

condition of the host, method of delivery, and other factors known to those skilled in the art, and will be of sufficient quantity to raise blood ketone levels to a degree required to treat and prevent Alzheimer's Disease. Derivatives of L-carnitine which may be used in the present invention include but are not limited to decanoylcarnitine, hexanoylcarnitine, caproylcarnitine, lauroylcarnitine, octanoylcarnitine, stearoylcarnitine, myristoylcarnitine, acetyl-L-carnitine, O-Acetyl-L-carnitine, and palmitoyl-L-carnitine.

Therapeutically effective amounts of the therapeutic agents can be any amount or dose sufficient to bring about the desired anti-dementia effect and depend, in part, on the severity and stage of the condition, the size and condition of the patient, as well as other factors readily known to those skilled in the art. The dosages can be given as a single dose, or as several doses, for example, divided over the course of several weeks.

In one embodiment, the MCT's or fatty acids are administered orally. In another embodiment, the MCT's are administered intravenously. Oral administration of MCT's and preparations intravenous MCT solutions are well known to those skilled in the art.

Oral and intravenous administration of MCT or fatty acids result in hyperketonemia. Hyperketonemia results in ketone bodies being utilized for energy in the brain even in the presence of glucose. Additionally, hyperketonemia results in a substantial (39%) increase in cerebral blood flow (Hasselbalch et al. 1996). Hyperketonemia has been reported to reduce cognitive dysfunction associated with systemic hypoglycemia in normal humans (Veneman et al. 1994). Please note that systemic hypoglycemia is distinct from the local defects in glucose metabolism that occur in AD. In another embodiment, the invention provides the subject compounds in the form of one or more prodrugs, which can be metabolically converted to the subject compounds by the recipient host. As used herein, a prodrug is a compound that exhibits pharmacological activity after undergoing a chemical transformation in the body. The said prodrugs will be administered in a dosage required to increase blood ketone bodies to a level required to treat and prevent the occurrence of Alzheimer's Disease. A wide variety of prodrug formulations are known in the art. For example, prodrug bonds may be hydrolyzable, such as esters or anhydrides, or enzymatically biodegradable, such as amides.

This invention also provides a therapeutic agent for the treatment or prevention of dementia of Alzheimer's type, or other loss of cognitive function caused by reduced neuronal metabolism, comprising medium chain triglycerides. In a preferred embodiment, the therapeutic agent is provided in administratively convenient formulations of the compositions including dosage units incorporated into a variety of containers. Dosages of the MCT are preferably administered in an effective amount, in order to produce ketone body concentrations sufficient to increase the cognitive ability of patients afflicted with AD or other states of reduced neuronal metabolism. For example, for the ketone body D-beta-hydroxybutyrate, blood levels are raised to about 1-10 mM or as measured by urinary excretion in the range of about 5 mg/dL to about 160 mg/dL, although variations will necessarily occur depending on the formulation and host, for example. Effective amount dosages of other MCTs will be apparent to those skilled in the art. Convenient unit dosage containers and/or formulations include tablets, capsules, lozenges, troches, hard candies, nutritional bars, nutritional drinks, metered sprays, creams, and suppositories, among others. The compositions may be combined with a pharmaceutically acceptable excipient such as gelatin, an oil, and/or other pharmaceutically active agent(s). For example, the compositions may be advantageously combined and/or used in combination with other therapeutic or prophylactic agents, different from the subject compounds. In many instances, administration in conjunction with the subject compositions enhances the efficacy of such agents. For example, the compounds may be advantageously used in conjunction with antioxidants, compounds that enhance the efficiency of glucose utilization, and mixtures thereof, (see e.g. Goodman et al. 1996).

In a preferred embodiment the human subject is intravenously infused with MCT, MCFA (medium chain fatty acids) and/or ketone bodies directly, to a level required to treat and prevent the occurrence of Alzheimer's Disease. Preparation of intravenous lipid, and ketone body solutions is well known to those skilled in the art.

In a preferred embodiment, the invention provides a formulation comprising a mixture of MCT and carnitine to provide elevated blood ketone levels. The nature of such formulations will depend on the duration and route of administration. Such formulations will be in the range of 0.5 g/kg/day to 10 g/kg/day of MCT and 0.5 mg/kg/day to 10 mg/kg/day of carnitine or its derivatives,. Variations will necessarily occur depending on the formulation and/or host, for example.

A particularly preferred formulation comprises a range of 10-500 g of emulsified MCT combined with 10-2000 mg of carnitine. An even more preferred formulation comprises 50 g MCT (95% triC8:0) emulsified with 50 g of mono- and di-glycerides combined with 500 mg of L-carnitine. Such a formulation is well tolerated and induces hyperketonemia for 3-4 hours in healthy human subjects.

In another embodiment, the invention provides the recipient with a therapeutic agent which enhances endogenous fatty acid metabolism by the recipient. The said therapeutic agent will be administered in a dosage required to increase blood ketone bodies to a level required to treat and prevent the occurrence of Alzheimer's Disease. Ketone bodies are produced continuously by oxidation of fatty acids in tissues that are capable of such oxidation. The major organ for fatty acid oxidation is the liver. Under normal physiological conditions ketone bodies are rapidly utilized and cleared from the blood. Under some conditions, such as starvation or low carbohydrate diet, ketone bodies are produced in excess and accumulate in the blood stream. Compounds that mimic the effect of increasing oxidation of fatty acids will raise ketone body concentration to a level to provide an alternative energy source for neuronal cells with compromised metabolism. Since the efficacy of such compounds derives from their ability to increase fatty acid utilization and raise blood ketone body concentration they are dependent on the embodiments of the present invention.

From the description above, a number of advantages of the invention for treating and preventing Alzheimer's Disease become evident:

(a) Prior art on AD has largely focused on prevention and clearance of amyloid deposits. The role of these amyloid deposits in AD remains controversial and may only be a marker for some other pathology. The present invention provides a novel route for treatment and prevention of AD based on alleviating the reduced neuronal metabolism associated with AD, and not with aspects of amyloid accumulation.

(b) Current treatments for AD are merely palliative and do not address the reduced neuronal metabolism associated with AD. Ingestion of medium chain triglycerides as a nutritional supplement is a simple method to provide neuronal cells, in which glucose metabolism is compromised, with ketone bodies as a metabolic substrate.

(c) Increase blood levels of ketone bodies can be achieved by a diet rich in medium chain triglycerides.

(d) Medium chain triglycerides can be infused intravenously into patients.

(e) Levels of ketone bodies can be easily measured in urine or blood by commercially available products (i.e. Ketostix®, Bayer, Inc.).

Accordingly, the reader will see that the use of medium chain triglycerides (MCT) or fatty acids as a treatment and preventative measure of Alzheimer's Disease (AD) provides a novel means of alleviating reduced neuronal metabolism associated with AD. It is the novel and significant insight of the present invention that use of MCT results in hyperketonemia which will provide increased neuronal metabolism for diseases associated with reduced neuronal metabolism, such as AD, ALS, Parkinson's Disease and Huntington's Disease. Although the description above contains many specificities, these should not be construed as limiting the scope of the invention but merely as providing illustrations for some of the presently preferred embodiments of this invention. For example, supplementation with MCT may prove more effective when combined with insulin sensitizing agents such as vanadyl sulfate, chromium picolinate, and vitamin E. Such agents may function to increase glucose utilization in compromised neurons and work synergistically with hyperketonemia. In another example MCT can be combined with compounds that increase the rates of fatty acid utilization such as L-carnitine and its derivatives. Mixtures of such compounds may synergistically increase levels of circulating ketone bodies.

Thus the scope of the invention should be determined by the appended claims and their legal equivalents, rather than by the examples given.

REFERENCES

Throughout the specification, citations to a number of references have been made. Each of these references is incorporated by reference herein in its entirety. Many of the references are summarized here:

Beffert, U., Danik, M., Krzywkowski, P., Ramassamy, C., Berrada, F., and Poirier, J. (1998) The neurobiology of apolipoproteins and their receptors in the CNS and Alzheimer's disease. *Brain Res Brain Res Rev* **27**:119-42.

Blass, J. P., and Zemcov, A. (1984) Alzheimer's disease. A metabolic systems degeneration? *Neurochem Pathol* **2**:103-14.

Craft, S., Newcomer, J., Kanne, S., Dagogo-Jack, S., Cryer, P., Sheline, Y., Luby, J., Dagogo-Jack, A., and Alderson, A. (1996) Memory improvement following induced hyperinsulinemia in Alzheimer's disease. *Neurobiol Aging* **17**:123-30.

Corbo, R.M. and Sacchi, R. (1999) Apoliporpotein E (APOE) allele distribution in the world. Is APOE*4 a 'thrifty' allele. *Ann Hum Genet* **63**:301-10.

Davis, J. N., and Chisholm, J. C. (1999). Alois Alzheimer and the amyloid debate. *Nature* **400**:810.

Edmond, J. (1992) Energy metabolism in developing brain cells. Can J Physiol Pharmacol **70**:S118-29.

Evans, D. A., Funkenstein, H. H., Albert, M. S., Scherr, P. A., Cook, N. R., Chown, M. J., Hebert, L.E., Hennekens, C.H., and Taylor, J. O. (1989) Prevalence of Alzheimer's disease in a community population of older persons. Higher than previously reported. JAMA **262**:2551-6.

Finch, C. E., and Cohen, D. M. (1997) Aging, metabolism, and Alzheimer disease: review and hypotheses. *Exp Neurol* **143**:82-102.

Frolich, L., Blum-Degen, D., Bernstein, H. G., Engelsberger, S., Humrich, J., Laufer, S., Muschner, D., Thalheimer, A., Turk, A., Hoyer, S., Zochling, R., Boissl, K. W., Jellinger, K., and Riederer, P. (1998) Brain insulin and insulin receptors in aging and sporadic Alzheimer's disease. *J Neural Transm* ***105***:423-38.

Gregg, R. E., Zech, L. A., Schaefer, E. J., Stark, D., Wilson, D., and Brewer, H. B. Jr . (1986). Abnormal in vivo metabolism of apolipoprotein E4 in humans. J Clin Invest **78**:815-21.

Goodman, L. S., Limbird, L. E., Milinoff, P. B., Gilman, A. G., and Hardman, J. G. (editors). (1996). The Pharmacological Basis of Therapeutics, 9.sup.th Ed., McGraw-Hill.

Hall K., Gureje O., Gao S., Ogunniyi A., Hui S.L., Baiyewu O., Unverzagt F.W., Oluwole S., Hendrie H.C. (1998) Risk factors and Alzheimer's disease: a comparative study of two communities. Aust N Z J Psychiatry **32**:698-706.

Hamosh, M. (1990) In: Lingual and Gastric Lipases: Their role in fat digestion. CRC press, Boca Raton, FL.

Hanlon C.S., and Rubinsztein D.C. (1995) Arginine residues at codons 112 and 158 in the apolipoprotein E gene correspond to the ancestral state in humans. Atherosclerosis **112**:85-90.

Hasselbalch, S. G., Madsen, P. L., Hageman, L. P., Olsen, K. S., Justesen, N., Holm, S., and Paulson, O. B. (1996) Changes in cerebral blood flow and carbohydrate metabolism during acute hyperketonemia. Am J Physiol **270**:E746-51.

Hoyer, S. (1998) Is sporadic Alzheimer disease the brain type of non-insulin dependent diabetes mellitus? A challenging hypothesis. *J Neural Transm* **105**:415-22.

Hoyer, S. (1992) Oxidative energy metabolism in Alzheimer brain. Studies in early-onset and late-onset cases. Mol Chem Neuropathol **16**:207-24.

Jolles, J., Bothmer, J., Markerink, M., and Ravid, R. (1992) Phosphatidylinositol kinase is reduced in Alzheimer's disease. *J Neurochem* **58**:2326-9.

Kolanowski, J., Young, J. B., and Landsberg L. (1994) Stimulatory influence of D(-)3-hydroxybutyrate feeding on sympathetic nervous system activity in the rat. Metabolism **43**:180-5.

Klivenyi, P., Ferrante, R. J., Matthews, R. T., Bogdanov, M. B., Klein, A. M. Andreassen, O. A., Mueller, G., Wermer, M., Kaddurah-Daouk, R., and Beal, M. F. (1999) Neuroprotective effects of creatine in a transgenic animal model of amyotrophic lateral sclerosis. *Nat. Med.* **5**:347-50.

Koo, E. H., Lansbury, P. T., Jr., and Kelly, J. W. (1999) Amyloid diseases: abnormal protein aggregation in neurodegeneration. *Proc Natl Acad Sci U S A.* **96**:9989-90.

Knouff, C., Hinsdale, M. E., Mezdour, H., Altenburg, M. K., Watanabe, M., Quarfordt, S.H., Sullivan, P.M., and Maeda, N. (1999) Apo E structure determines VLDL clearance and atherosclerosis risk in mice. J Clin Invest **103**:1579-86.

Lannert, H., and Hoyer, S. (1998) Intracerebroventricular administration of streptozotocin causes long- term diminutions in learning and memory abilities and in cerebral energy metabolism in adult rats. *Behav Neurosci* **112**:199-208.

Loktionov A., Vorster H., O'Neill I.K., Nell T., Bingham S.A., Runswick S.A., Cummings J.H. (1999) Apolipoprotein E and methylenetetrahydrofolate reductase genetic polymorphisms in relation to other risk factors for cardiovascular disease in UK Caucasians and Black South Africans. Atherosclerosis **145**:125-35.

Mattson, M.P. (1998). Experimental models of Alzheimer's Disease. *Science and Medicine* March/April:16-25.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., and Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**:939-44.

Meier-Ruge, W., Bertoni-Freddari, C., and Iwangoff, P. (1994) Changes in brain glucose metabolism as a key to the pathogenesis of Alzheimer's disease. Gerontology **40**:246-52.

Messier, C., and Gagnon, M. (1996) Glucose regulation and cognitive functions: relation to Alzheimer's disease and diabetes. *Behav Brain Res* **75**:1-11.

Neve, R. L., and Robakis, N. K. (1998) Alzheimer's disease: a re-examination of the amyloid hypothesis. *Trends Neurosci* **21**:15-9.

Nishimura, M., Yu, G., and St George-Hyslop, P. H. (1999) Biology of presenilins as causative molecules for Alzheimer disease. *Clin Genet* **55**:219-25.

Odle, J. (1997) New insights into the utilization of medium-chain triglycerides by the neonate: Observations from a pig model. *J Nutr.* **127**:1061-7.

Reiman, E. M., Caselli, R. J., Yun, L. S., Chen, K., Bandy, D., Minoshima, S., Thibodeau, S. N., and Osborne, D. (1996) Preclinical evidence of Alzheimer's disease in persons homozygous for the epsilon 4 allele for apolipoprotein E. *N Engl J Med 334*:752-8.

Ogawa, M., Fukuyama, H., Ouchi, Y., Yamauchi, H., and Kimura, J. (1996) Altered energy metabolism in Alzheimer's disease. J Neurol Sci **139**:78-82.

Osuntokun B.O., Sahota A., Ogunniyi A.O., Gureje O., Baiyewu O., Adeyinka A., Oluwole S.O., Komolafe O., Hall K.S., Unverzagt F.W., et al (1995) Lack of an association between apolipoprotein E epsilon 4 and Alzheimer's disease in elderly Nigerians. Ann Neurol 38:463-5.

Roheim P.S., Carey M., Forte T., and Vega G. L. (1979) Apolipoproteins in human cerebrospinal fluid. Proc Natl Acad Sci U S A **76**:4646-9.

Selkoe, D. J. (1994) Alzheimer's Disease: A central role for amyloid. *J. Neruopathol. Exp. Neruol.* **53**:438-447.

Selkoe, D. J., (1999) Translating cell biology into therapeutic advances in Alzheimer's disease. *Nature* **399**:A23-31.

Simpson, I. A., and Davies, P. (1994) Reduced glucose transporter concentrations in brains of patients with Alzheimer's disease: Ann Neurol **36**:800-1.

Swaab, D. F., Lucassen, P. J., Salehi, A., Scherder, E. J., van Someren, E. J., and Verwer, R. W. (1998) Reduced neuronal activity and reactivation in Alzheimer's disease. *Prog Brain Res* **117**:343-77.

Veneman, T., Mitrakou, A., Mokan, M., Cryer, P., and Gerich, J. (1994) Effect of hyperketonemia and hyperlacticacidemia on symptoms, cognitive dysfunction, and counterregulatory hormone responses during hypoglycemia in normal humans. Diabetes **43**:1311-7.

Zekraoui L., Lagarde J.P., Raisonnier A., Gerard N., Aouizerate A., Lucotte G. (1997) High frequency of the apolipoprotein E *4 allele in African pygmies and most of the African populations in sub-Saharan Africa. Hum Biol 69:575-81.

Zubenko, G. S., Stiffler, J. S., Hughes, H. B., and Martinez, A. J. (1999) Reductions in brain phosphatidylinositol kinase activities in Alzheimer's disease. *Biol Psychiatry* **45**:731-6.

EXAMPLES

The following example is offered by way of illustration and not by way of limitation.

Example 1: Nutritional drink

Nutritional drinks are prepared using the following ingredients: emulsified MCT 100 gr/drink, L-carnitine 1gram/drink, mix of daily vitamins at recommended daily levels, and a variety of flavorings.

Example 2: Additional formulations

Additional formulations can be in the form of Ready to Drink Beverage, Powdered Beverages, Nutritional drinks, Food Bars, and the like. Formulations for such are clear to those skilled in the art.

A. Ready to Drink Beverage Ready to Drink Beverages are prepared using the following ingredients: emulsified MCT 5-100 g/drink, L-carnitine 250-1000 mg/drink, and a variety of flavorings and other ingredients used to increased palatability, stability, etc.

B. Powdered Beverages MCT may be prepared in a dried form, useful for food bars and powdered beverage preparations. A powdered beverage may be formed

from the following components: dried emulsified MCT 10-50 g, L-carnitine 250-500 mg, sucrose 8-15 g, maltodextrin 1-5 g, flavorings 0-1 g.

C. Food bar A food bar would consist of: dried emulsified MCT 10-50 g, L-carnitine 250-500 mg, glycerin 1-5 g, corn syrup solids 5-25 g, cocoa 2-7g, coating 15-25 g.

D. Gelatin Capsules Hard gelatin capsules are prepared using the following ingredients: MCT 0.1-1000 mg/capsule, L-carnitine 250-500 mg/capsule, Starch, NF 0-600 mg/capsule; Starch flowable powder 0-600 mg/capsule; Silicone fluid 350 centistokes 0-20 mg/capsule. The ingredients are mixed, passed through a sieve, and filled into capsules.

E. Tablets Tablets are prepared using the following ingredients: MCT 0.1-1000 mg/tablet; L-carnitine 250-500 mg/tablet; Microcrystalline cellulose 20-300 mg/tablet; Starch 0-50 mg/tablet; Magnesium stearate or stearate acid 0-15 mg/tablet; Silicon dioxide, fumed 0-400 mg/tablet; silicon dioxide, colloidal 0-1 mg/tablet, and lactose 0-100 mg/tablet. The ingredients are blended and compressed to form tablets.

F. Suspensions Suspensions are prepared using the following ingredients: 0.1-1000 mg MCT; 250-500 mg L-carnitine; Sodium carboxymethyl cellulose 50-700 mg/5 ml; Sodium benzoate 0-10 mg/5 ml; Purified water 5 ml; and flavor and color agents as needed.

G. Parenteral Solutions A parenteral composition is prepared by stirring 1.5% by weight of MCT and L-carnitine in 10% by volume propylene glycol and water. The solution is made isotonic with sodium chloride and sterilized.